RIsk of nephrotoxic acute kidney injury associates to urinary levels of GM2AP

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Introduction

Acute kidney injury (AKI) occurs in response to certain drugs, metals and a variety of other insults, however, AKI is nowadays diagnosed when the patient presents evident alterations of renal excretory, which show clinically detectable signs and symptoms (e.g. increased serum creatinine, proteinuria, etc.), at this a point, the damage is very extensive and the treatment very difficult. GM2AP is an 18-24 kDa substrate cofactor for lysosomal β-hexosaminidase, implicated in GM2 ganglioside metabolism.

Aims

The aim of this work is studying the relation between urinary excretion GM2AP and acquired predisposition to acute kidney injury from nefhrotoxic.

Methods/ experimental design

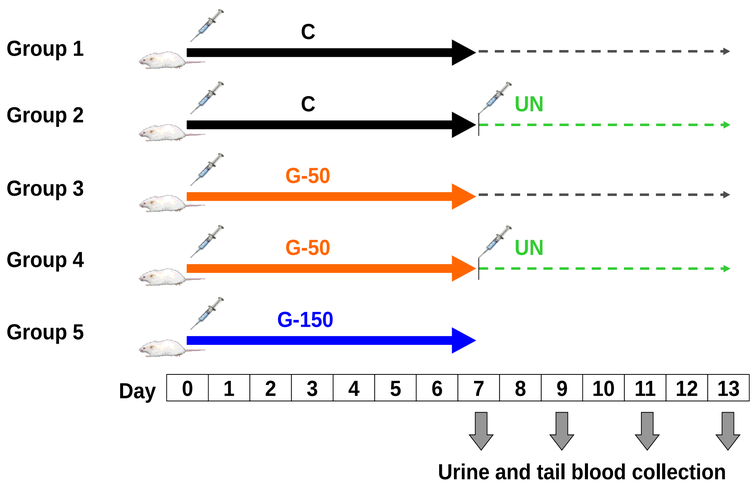
- Experimental Groups (Wistar rats weighing 190-220 g):

- **Group 1: daily saline (C) i.p. (day 0 to 13)**
- **Group 2: daily saline i.p. (day 0 to 13), plus one i.p. dose of Uranyl Nitrate (UN) 0,5 mg/kg at day 7.**
- **Group 3: daily 50 mg/kg body weight Gentamicin (G-50) i.p. (day 0 to 6), and daily saline i.p. (day 7 to 13).**
- **Group 4: same as Group 3 plus one i.p. dose of Uranyl Nitrate (UN) 0,5 mg/kg at day 7.**
- **Group 5: daily 150 mg/kg body weight Gentamicin (G-150) i.p. (day 0 to 6).**

-Renal toxicity was evaluated by measuring plasma creatinine and creatinine clearance urine proteins and N-acetyl-glucosaminidase (NAG) and hematoxylin eosin staining. Western blot were used to investigate the presence of novel urine markers.

-Human samples: The urine and blood from eight unselected patients treated for at least 3 days with gentamicin, and the urine from eight sex- and agematched untreated individuals.

Schematic representation of the experimental design



Conclusions

Subnefrotoxic treatment with gentamcin predisposes rats to acute renal failure, this predisposition is evidenced by exposure to a second sub-nephrotoxic agent. Increased urine levels of GM2AP from the onset of a gentamicin regime will provide means of detecting the increasing risk of an AKI burst as a consequence of further gentamicin administration or treatment with another potential nephrotoxicant.

Results

Evolution of biomarkers during treatment with gentamicin

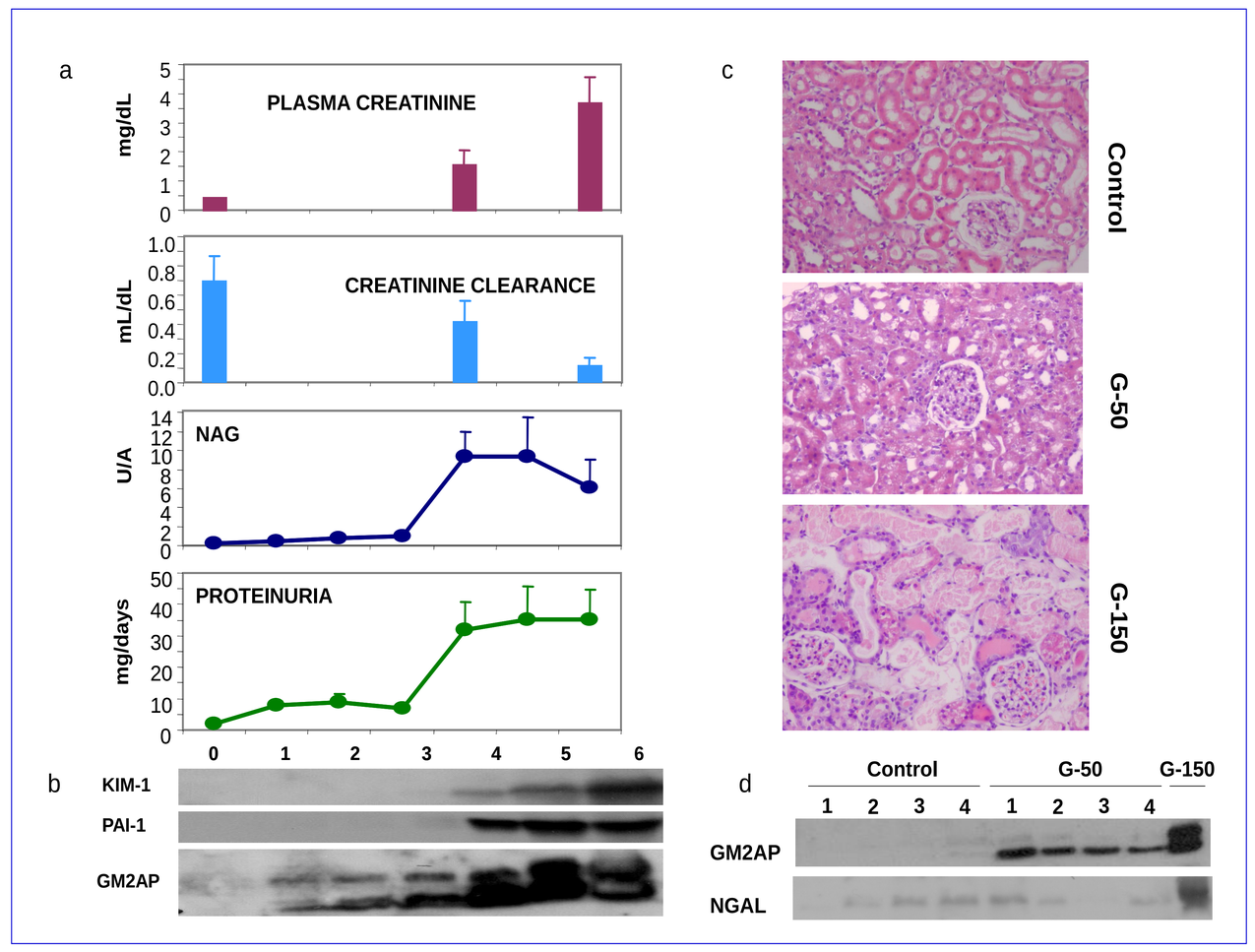
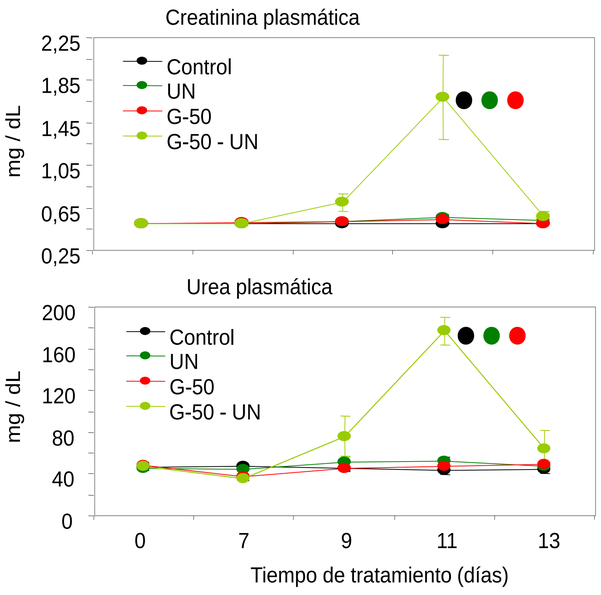


Figure 1. Evolution of GM2AP and biomarkers of AKI. (a) Evolution of plasma creatinine concentration, creatinine clearance, proteinuria and N-acetyl-glucosaminidase (NAG), (b) representative images of western blot analysis of plasminogen activator inhibitor 1 (PAI-1), kidney injury molecule 1 (KIM-1) and GM2AP levels in urine, over time and (d) NGAL and GM2AP from three randomly selected animals from C, G-50, and G-150 groups. Representative images (400X) of the cortex of hematoxilin–eosin-stained renal sections from C, G-50, and G-150 rats (n=6) (c).

Subnefhrotoxic doses of gentamicin predisposes to acute renal failure



	Pacientes sanos								Pacientes tratados con gentamicina							
	1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8
Sexo	M	F	F	F	F	M	M	F	M	F	F	F	F	F	F	M
Edad	23	23	29	33	43	61	64	74	23	24	30	38	45	61	68	74
Peso (kg)	73	70	50	66	53	59	80	50			60		63	65.5	60	61
Crpl (mg/dL)									0.93	0.74	0.71	0.8	0.7	0.69	0.79	0.6
Urea (mg/dL)									30	10	12	23	49	21	34	25
MDRD													91		72	118
C-G (ml/min)									109	117	110		100	89	64	93

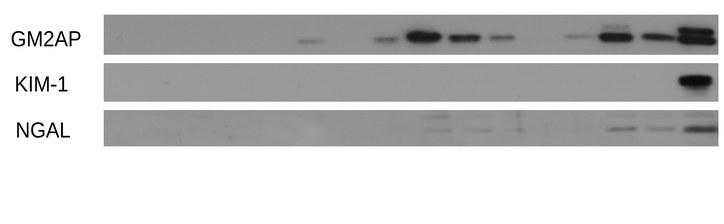


Figure 2. Sub-nephrotoxic gentamicin sensitizes to acute renal failure. (a) Time-course evolution of plasma creatinine and BUN concentration, of rats treated as indicated in experimental group ; n=6. (b) Representative images of western blot analysis of GM2AP, NGAL, and kidney injury molecule 1 (KIM-1) in the urine of eight patients treated with gentamicin and eight sex- and age-matched untreated individuals. Their gender, age, weight, plasma creatinine concentration (Crpl), blood urea concentration, and glomerular filtration rate estimated by the Modification of Diet in Renal Disease (MDRD) study equation or the Cockroft–Gault (C–G) equation are provided (when known).

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